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Tropical ulcer

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TROPICAL ULCER

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TROPICAL ULCER

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INTRODUCTION

Tropical ulcer presents itself as an interesting disease in several respects. Its etiological relationship to Vincent's angina, noma or gangrenous stomatitis and hospital gangrene of the temperate zones is significant, both as to causative organisms and predisposing factors.

In the tropics the ulcer is of economic importance. Loewenthal (27) considers it one of the great causes of death among Africans and Clements (8) claims it is the greatest single cause of morbidity amongst the natives of Australia's island colonies. He reported that in New Guinea labor has been reduced as much as 10% by tropical ulcer. Lloyd Patterson (35) described one epidemic which, "swept like a plague up the whole of Assam", interfered with the efficiency of the labor of the coolies in the tea gardens. The disease was common among carriers attached to the East African forces during the Great War. Treatment and healing are usually slow and tedious, often requiring long periods

of hospitalization where hospital space is scarce and helpers are few.

As early as the sixties of the last century, tropical ulcer was a recognized entity, but not until the beginning of the present century has much attention been paid to it. The fact that tropical ulcer was, for many years, not differentiated from many other types of tropical sores, as yaws and syphilis, has confused the picture to a great extent. Since the turn of the century, excellent though comparatively limited research has been conducted on both the etiological factors and the treatment of this disease, however, much still remains to be learned.

DEFINITION. Tropical ulcer is an acute gangrenous sloughing ulcer with a foul fetid odor of phagedenic character, which may spread to bone and muscle, and usually occurs on the legs below the knee. It may arise spontaneously or be superimposed upon a pre-existing wound. It is the result of invasion of tissues by a group of micro-organisms after these tissues have been changed by certain predisposing causes. The ulcer almost invariably becomes chronic. Spontaneous healing may occur, but ordinarily without early and vigorous treatment, much tissue destruction and structural deformity may result.

SYNONYMS. Tropical ulcer is known under

nearly as many names as there are localities where it has been found. Some of these are Aden ulcer, Annom ulceration, Cachan boil, Delago sore, Mozambique sore, Naga sore, Rhodesian sore, Zambesia sore, Yomen sore, and Natal sore. Other terms are phagedena Tropica and ulcere Tropicale (Italian), tropiche Phagedenismus (German), ulcère phegédeneque des pays chauds (French) and Ulcerum Tropicium.

SYMPTOMATOLOGY

For many years tropical ulcer was the diagnostic garbage heap of tropical medicine. Anything which did not respond immediately to arsenic was dropped into that class. Tropical ulcer is an acute condition which runs a rapid course and which, if not treated sufficiently, almost always develops into a chronic indolent sore, which does not differ from other indolent ulcers of the tropic or temperate zones, except that it is the sequel of a specific pathogenic process. This fact is frequently overlooked by workers in the tropics, who continue to class all indolent ulcers as tropical ulcers, and this accounts for the variations in clinical descriptions, bacteriology, and histopathology that are to be found in the literature.

Neither is there one cause common to all ulcers in the tropics. (27) A septic wound will become an ulcer, a boil which has burst and then become contaminated will form an ulcer. Some ulcers may have a yaws origin, and others may occur in a general disease as in the cases of sepsis neonatorum. But apart from these, there is the true "tropical ulcer". In a native's mind the former group of ulcers is not counted as of much consequence, though treatment will be sought. Some of these are even counted beneficial in that they "let out the bad". The latter group of

tropical ulcer, however, is dreaded, as it can be fatal. This ulcer, while it may follow a small wound, frequently rises spontaneously.

CLINICAL APPEARANCE. Clements (7) describes the appearance of tropical ulcer as being circular or oval in outline with ragged edges which are slightly raised and slope at an acute angle to the base. They are not clear-cut as the "punched out" syphilitic ulcer. The ulcers vary in size from about one-half square inch to 13½ square inches. Adams (1) says that the depth is in inverse proportion to the extent of the ulceration, but the smaller ulcers penetrate deeper than the skin only occasionally. The edges have an undermined appearance due to small penetrating sinuses. The base is covered with a slough, yellow to grey, which in new lesions fills the whole of the area and rises above the edges. In ulcers of long standing the slough is only around the mouths of the sinuses and the base is clear. The slough is hard to remove and when it is removed a red bleeding granulation tissue is revealed. The ulcer has a foul fetid odor which is characteristic of fusiform bacillus infections. Loewenthal (27) says the general aspect of the ulcer is one of necrosis rather than one of inflammation. Eggers (13) describes the appearance of the ulcer in China and it corresponds very closely to Clements' description. Eggers says it

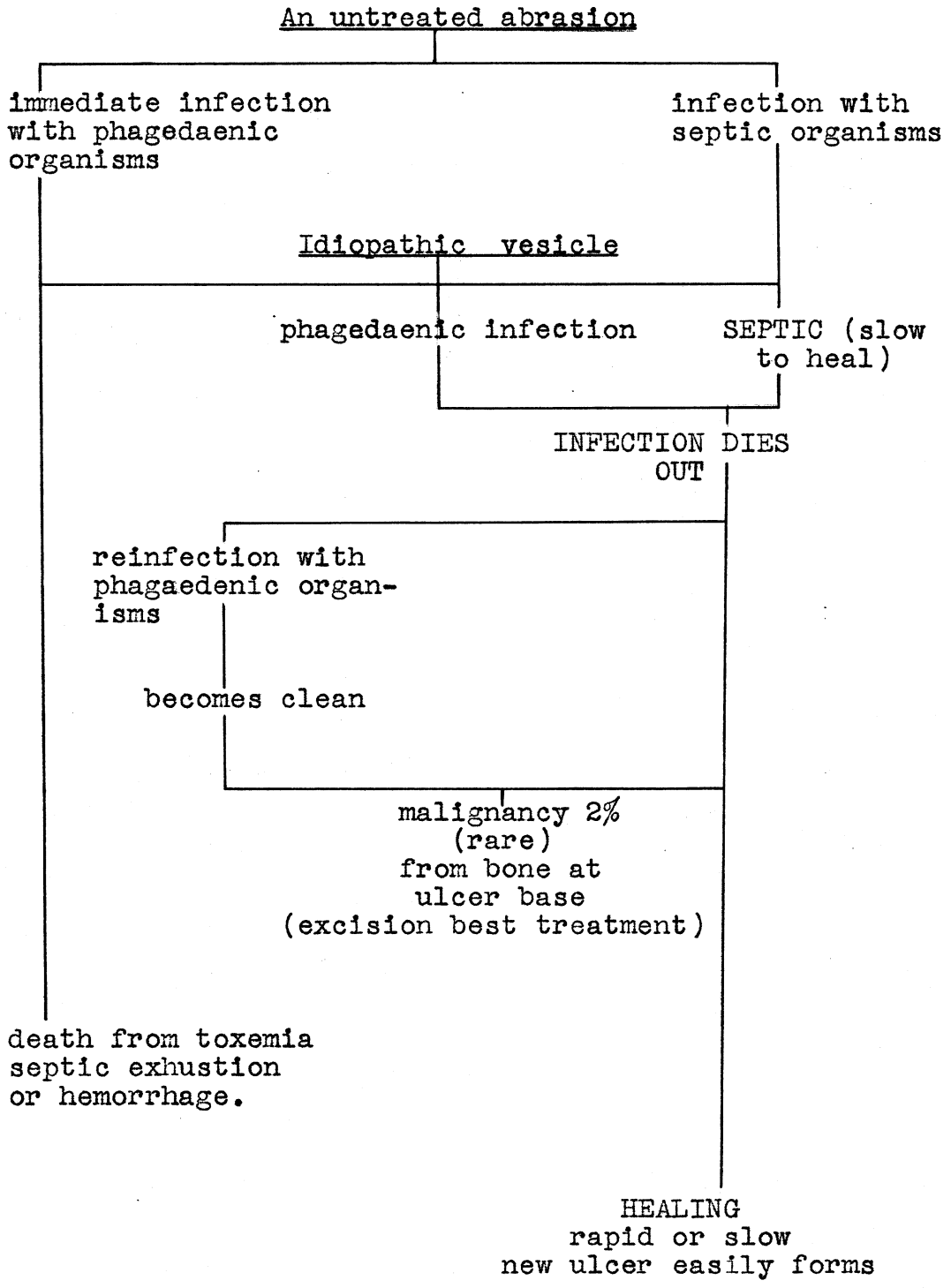
is a smooth, deeply marginated sore with the edges somewhat infiltrated. The ground or base is covered with a grayish foul-smelling slough which when detached leaves an easily bleeding granulation tissue. He also states that great pain is a most constant feature. Innes (21) from India describes tropical ulcer as an "acute-looking ulcer of long duration". It has deep and punched out undermined edges, an abundant discharge of glairy mucous with freely bleeding, sometimes pearly, islets which are engorged and project through the base. She describes an extreme hypersensitivity with pain which often radiates up the limb. Manson (29) says that in bad cases muscles, tendons, nerves, vessels and the periosteum of bone may be involved. Joints, bones, and large blood vessels may be destroyed causing deformities such as ankylosis, strangulation of parts, and cicatrix. Clements (9) states that in these deeper involvements the only organisms found were pyogens while fuso-spirochaetal processes are confined to the epithelium, subcutaneous tissue, and fat.

The ulcer is seen on exposed parts of the body such as legs, ankles and feet. A few may appear on the hands and forearms. The majority are found on the anterior aspect of the leg and in the middle and lower third and on the dorsum of the foot. The ulcer may also be located on the medial and lateral malleolus

and lower half of the tendon achilles. These ulcers are usually single, although more than one have been seen on one patient. Several may also be seen in one family.

Clements (9) finds a correlation between the distribution of the blood supply of the lower extremities and the site of the ulcer. He has observed that the ulcers usually occur in areas supplied by terminal vessels of the main arteries. The failure of these vessels to overlap completely may explain the insufficiency of the blood supply to these sites. Woodland and Weddel (46) have shown that the adventitia of the blood vessels of the lower third of the leg is very richly supplied with vasoconstrictor fibers. This further reduces the amount of blood available to the tissues of the leg, as compared with that available for the tissues of the arm. This should, no doubt, partly explain the high percentage of ulcers on the leg. On examination of the legs of many natives in New Guinea, Clements found patches of smooth shiny skin from which the hair had disappeared. These were not scars, but resembled areas which neurologists several decades ago would have attributed to trophic nerve degeneration. Although evidence could not be obtained that ulcers invariably developed in this type of skin, it was observed that large numbers did occur in these areas.

SEQUENCE OF EVENTS IN THE PATHOLOGY
OF A TROPICAL ULCER



(As copied from James (23).)

There is a type of tropical ulcer which occurs on or near and around the finger and toe nails. This will be discussed more fully presently.

It is the general consensus of opinion that tropical ulcer may begin from a pre-existing local injury or from a small papule which may arise either spontaneously or may be the result of an insect bite.

(9) In ulcers secondary to trauma, infected wound, burns, or some other type of sore as yaws or septic sore, the process of the infection appears first as an increase in the amount of discharge of the original lesion so that a portion of the wound's edge assumes the appearance of a tropical ulcer. The remainder of the traumatized area usually becomes involved sooner or later.

The ulcers beginning without pre-existing lesions appear as small itchy painful papules under the skin about the size of a mosquito bite (1). Others described it as an idiopathic vesicle or a dark painful blister (23). This bleb may remain stationary for several days or may increase in size immediately. Whenever it begins, the increase is very rapid and the dome of the bleb may be lost over night leaving the characteristic ulcer (9). The itching and discomfort give place to pain which steadily and greatly increases, in some instances, out of all proportion to the size of

the lesion. Before the bleb breaks down the color changes rapidly from a dusky red to almost black. If the papule is cut into at this stage when it is black, soft and painful, one finds a small necrotic mass which has not yet burst through the skin. The lesion resembles a small angry furuncle, except for the color. The papule may break down in one or two days and has a raw, angry, sloughing surface. The edges begin to elevate and the surrounding skin is undermined by pus. The sloughing subcutaneous tissue and the true skin separate. At this stage the ulcer is the most painful. For two or three days a thick, brownish, bloody, tenacious, foul-smelling pus is exuded and is followed by a thinner, more abundant discharge which is no less foul in nature. The spread may be rapid, increasing in size by as much as a finger's breadth a day or in three weeks time it may have developed a circumference of from three to ten centimeters. The developmental stage may only last about four or five days and after that extension is, as a rule, limited to clefts and undermined edges. At times two ulcers may coalesce, but this is not common. The undermined edges soon become elevated and hardened, forming cord-like edges which are sclerotic. The exudate finally becomes a foul smelling, greyish, semi-fluid pus which forms a pseudomembrane covering the dirty greyish to reddish granulations at the base

of the ulcer (5). As the ulcer reaches a point of equilibrium with the surrounding tissue it usually takes on the appearance of a chronic septic ulcer. There may be no sign of healing and the ulcer may remain stationary for a long time. Occasionally it may heal in a comparatively short time, but it is usually only after a long period of years, if at all, that healing takes place in the untreated ulcer. The scar which develops with the healing ulcer is usually tender and weak and easily breaks down again, probably because it holds the responsible organisms dormant in its interstices. Furthermore, blood supply to the area is diminshed both because of scar tissue formation and the obliterative endoarteritis which takes place (23). Therefore, it is not hard to understand why recurrences are so common.

Many of these ulcers, however, go on to a phagedenic nature. After an interval the ulcer will spread to a greater depth, destroying subcutaneous tissue and the muscle and often attacking the underlying bone. It may give rise to periostitis and osteitis. Osteomyelitis may develop, but the process usually remains more superficial. The whole foot may be swollen resembling elephantiasis (5).

Ulcers are very chronic and may persist for years endangering the life or general health of the

patient. Judging by the number of scars seen above the tibia with thickening of the bone, it is evident that even large ulcers of long standing may suddenly heal. At other times the patients emaciate considerably, become completely crippled and, consequently, are confined to their homes and die of effects of the septic resorption (5).

Types of Tropical Ulcer: Tropical ulcer may be divided into several types. The following classification is based on that of Innes (21).

1. Acute Ulcer. (a) Acute rapidly spreading ulcer with cave-like extensions into the tissues and a great deal of discharge and exquisite pain.

(b) Acute fulminating ulcer or acute phagedaena. This type is associated with extensive and rapid tissue destruction not infrequently leading to a fatal termination. Cases of this variety usually occur in children under starvation conditions. In this type the elevation and the hard edges of the ulcer were not noticed and the ulcer seemed to be unlimited in its course (9).

2. Subacute Ulcer. Looks acute, but is in reality from eight to ten months old. There is pain and a hemorrhagic discharge.

3. Chronic Ulcer. Thickened edges and only

a little discharge. It slowly destroys soft tissue as well as bony tissue.

4. Phagedaenae of the Terminal Phalanges.

This type is described by Gunther (17) as occurring in the distal half of the terminal phalanges of the fingers and toes. It commences as a swelling around the nails, after which the tip of the finger rapidly becomes bulbous and then sloughs. When the slough is detached, the base of the nail remains firmly attached, but the skin and soft tissue as far back as the nail are missing, and the tip of the phalanx is seen projecting from the base of the ulcerated nail. In all types, once the sloughing has occurred and the tension is relaxed, the condition is practically painless. Loewenthal (21) describes even more advanced cases of phagedaena of the foot. He says the blackened necrosed stumps of the tarsal bones project from a mass of unhealthy granulations among which may be seen the mummified remains of muscles and tendons. The patient is cachectic and exhausted while the temperature remains normal or subnormal and general signs of pyogenic infection are absent.

There seems to be some discrepancy in the presence or degree of pain in tropical ulcer as described by various writers. But, if we consider Clements' (9) statement that in the acute recently formed ulcers there

is extreme pain and tenderness while in the chronic forms all sensation is lost, I believe most of the differences can be explained. In her classification Innes (21) makes the same observations as to the relationship of pain to the acute and chronic stages of the ulcer.

SYSTEMIC EFFECTS. All degrees of systemic effects from those of severe toxemia to nothing at all have been sited as accompanying tropical ulcer. Fever as high as 103° F. and 104° F. and regional glandular enlargement have been described by Innes (21) and James (23). Clements (9), however, states that he has seen fever only in very young children suffering from the acute form of the ulcer and that he believes the glandular enlargement to be due more to the secondary invading pyogens rather than to the causative organisms of tropical ulcer. Corpus (10) says that ulcers do not seem to give any trouble. The affected child goes about in the usual way. If the ulcer is kept clean, no pain is felt, nor does the odor of the discharge cause annoyance. The ulcers itch, however, and in many cases scratching increases their size.

Loewenthal (21) says that ulcers are very likely to produce an inferiority complex in many natives due to the repulsiveness of the sores, because they attract flies and have such a vile odor.

MORBIDITY AND MORTALITY. In Uganda (27) the morbidity of tropical ulcer is enormous. The precise extent of the disease is unknown, but at every hospital and dispensary in two districts, ulcers outnumber all other cases by more than two to one. If untreated, death nearly always follows. The morbidity and mortality of tropical ulcer is speculated to rank with malaria, plague and tripanisomiasis. Clements (7) says that tropical ulcer is the greatest single cause of morbidity among the natives of New Guinea, Papua and Australia's island colonies. He further states (9) that death from this disease is rare.

ETIOLOGY

A survey of the literature shows that there is great variation of opinion among authorities as to the exact etiology of tropical ulcer. Some believe that a single micro-organism may be responsible for the lesion while others think that a group of micro-organisms may be the causative agent. There are those who contend that tropical ulcer is actually a deficiency disease while the micro-organisms present are of only secondary importance. If a deficiency disease, the question arises as to what kind of a deficiency this might be. Is it of one or of all the vitamines or is it a calcium deficiency or is it due to some other factor? The consensus of opinion now is that both micro-organisms and predisposing body deficiencies are essential, since the disease is seldom found in the vigorous, well-fed and well-nourished individual and micro-organisms are invariably found in the lesions when looked for with care.

PREDISPOSING FACTORS. Manson (29) states that the concurrence of certain unknown conditions aside from micro-organisms are essential for tropical ulcer for it is most apt to attack the half-starved malaria-stricken pioneer in the jungles, the overdriven slave gang, and the soldier in the tropics. Corpus (10) from the Philippine Islands finds that it occurs in persons

who have been impaired in health by privations and unsanitary surroundings. Edges (12) reports cases of tropical ulcer in Europeans in the tropics which he believes to be due entirely to dietary deficiencies because when fresh vegetables and fish were supplied to Europeans in these regions the trouble was reduced 50%. He also observed that the disease occurred only among those Europeans who lived on restricted diets in the tropics.

Clements (9) has done a remarkable piece of research among the natives on various islands surrounding the mainland of Australia. He is one of those who holds both dietary and bacteriological factors as important in the etiology of the disease. He says "tropical ulcer is the result of the invasion by a group of micro-organisms of tissues that have been changed by certain predisposing causes which are of considerable importance in this disease. Outstanding among these predisposing conditions is diet". By carefully comparing the incidence of tropical ulcer among the inhabitants of a certain island where the diets of those living along the coast differed greatly from those further inland, Clements came to the conclusion that the disease is associated with either a complete or partial deficiency of the Vitamine B complex associated with a diet rich in carbohydrates and low in protein and fat. He

believes that this deficiency reduces the reduction potential of the tissues so that it falls below that of the invading organisms. These organisms then reduce the "oxygen-containing materials" in the tissues and thus obtain the oxygen necessary in an accessible form for their growth and propagation. This process fails to occur when the causal organisms are introduced into healthy skin because the potential of healthy skin is higher than that of the invading organisms.

An epidemic of tropical ulcer following the Great War in Syria was reported by Adams (1). He states that the worst cases were seen in men suffering from starvation edema in 1916. The epidemic persisted until 1922 and was particularly common among the poor. Although Adams makes no further comments on diet in his report it is reasonable to suppose that in a country such as Syria where in peace years the food supply of the poor is apt to be inadequate and unbalanced, that during the post war days these conditions were much worse and that this was probably an important factor in the ulcer epidemic.

A low blood calcium has been considered by some to be the prime etiological factor in tropical ulcer. Orr and Gilks (34), McCulloch (30) and Loewenthal (21), workers in Africa, all seem to favor this view. McCullouch reports in his finding a high blood

sugar and a low blood calcium and urea. He believes the ulcer to be of a diabetic nature and that causative organisms need not be considered at all. Loewenthal points out that in Africa the tropical ulcer is found almost exclusively among the poorest class. He says the well-to-do native is as susceptible to other diseases as the poorest and that the mode of living of these two classes is in most cases identical with the sole exception of diet. The chiefs and those who are more prosperous have more milk, meat and eggs. He backs this argument with theropeutic results which will be considered later. Clements (9) in his studies and extensive investigation at Manus found that the calcium content of the diet of those having tropical ulcer was, if anything, excessive. Ellis (14) from Africa also disagrees with Loewenthal and McCulloch, showing in his statistics as many ulcer patients with a high blood calcium as with a low blood calcium. We may be able to interpret Loewenthal's difference in diet as being one of protein deficiency rather than lack of calcium.

Geographical and climatic conditions appear to have a part in tropical ulcer incidence. A belt drawn around the globe between the 35th latitude north to the 10th latitude south would include almost all countries from which cases of tropical ulcer have been reported (9). It is common in most tropical countries

where it is hot and damp and where jungles flourish. In British New Guinea (5) tropical ulcer is found rarely among villages situated on high dry ground, while it is prevalent in those villages in the swampy muddy regions. Only a few cases have been reported from altitudes above 1,500 feet. In China (13) tropical ulcer is more common in the central portion than in either the north or south.

The incidence of tropical ulcer in relation to season agrees fairly well in most instances. From China (13), the Philippine Islands (10), and Australia (9) there is a reported increase in the disease during the rainy season or summer months when it is hot and damp. In the Pacific (23) the monsoon season with hot dry periods interrupted by drenching rains which kill the gardens is the ulcer season. Only in Syria (1) was the disease said to "flourish during the summer drought and never beginning in the rainy season". Here, however, the phrase summer drought suggest that with it might come food deficiencies or at least a limited supply of fresh vegetables and milk, which is doubtless of greater etiological significance than dry or wet weather.

There is a great discrepancy and variation reported as to age and sex incidence. This, however, seems to be due to a marked degree to the locality and

type of labor indulged in by the various ages and sexes. As, for instance, in the Gambia (45) the disease is most common among women and children who cultivate the rice field in the submerged land, and who care for the cattle and gather wood from the forests. As the male children outgrow these tasks their ulcers heal, while they persist in the girls through to womanhood. Clements (9), on the other hand, could find no great variation as to the age and sex incidence in Australia. He states that no age appears to be immune, but the active years from the ages of ten to forty supply the highest incidence. He also says that the more severe the type of ulcer, the less is the average age of the patient.

No race immunity is known. Tropical ulcer appears in all colors, races and creeds. It is found among Chinese, Assamese, South Americans, Melanesian, Polynesian and white settlers in the tropics who live on native diets for long periods of time.

In 1911 Le Danteg (11) sited two factors which he believed to be necessary to the development of tropical ulcer. These were abrasion of the skin and exposure of the abrasion to humid earth. At present the consensus of opinion is that gross macroscopic trauma or injury is a predisposing factor to tropical ulcer though not necessarily so. In an investigation in New Guinea (9) the incidence of tropical ulcer pre-

ceded by macroscopic trauma was high. Often tropical ulcer begins as a small swelling which suddenly develops into the ulceration. These may very likely be due to microscopic injury, such as insect bites or punctures due to spiney undergrowths. The ulcer (10) in the Philippine Islands was reported as being more common among the school children who were barefooted and whose feet often got wet and soiled with mud. This agrees with the incidence of tropical ulcer in the Gambia (45) mentioned above where trauma appears to be the predisposing factor among the women and children.

A great many tropical diseases have been listed as predisposing to tropical ulcer and "when this formidible list is examined", says Clements (9), "we find that these diseases, especially in the chronic state, lower vitality." Clements further states that he can see no particular relationship between tropical ulcer and malaria.

James (23), however, sees a very close relationship between malaria and tropical ulcer. He says that he has never seen tropical ulcer in the non-malarial white or in the foreigner who regularly takes his prophylactic quinine, although he has seen septic ulcers in these individuals. He tells of a certain island in the Pacific in the malarial belt, which, prior to 1933, was entirely free of malaria and the anopholes mosquitoes

and had absolutely no tropical ulcer. After 1933, mosquitoes, malaria and tropical ulcer were all common on the island. He says that malaria, due to its blood destroying power, toxic factors, and constant wastage of food materials prepares an ideal subject for the development of tropical ulcer.

A question of a relationship between syphilis, yaws, and tropical ulcer has, at times, arisen particularly in communities heavily infected with these diseases. If there be a relationship it is not understood at present. That these lesions have, at times, been mistaken for one another and incorrectly diagnosed is unquestionable, but it has also been suggested that a true tropical ulcer may arise from an old syphilitic or yaws sore as it may from any lesion.

BACTERIOLOGY. Although tropical ulcer has been recognized as a disease entity since about the middle of the last century, it was not until 1884 that Le Danteg (11) in Guinea described bacilli in the exudate form tropical ulcer. In 1907, twenty-three years later, Von Prowazek (31) in Java detected a spirochaete in the tropical ulcer. He called it Spirochaeta schaudinni, and Noguchi considered this spirochaete to be the same as Trepenoma vincenti. In 1909, two years later, Kysseletz and Mayer (26), working in German East Africa,

described quite fully the bacteriology of the disease. They described two types of fusiform bacilli and two varieties of spirochaetes. Assmy (2) in China described a fusiform bacillus and a spirochaete in tropical ulcer and Eggers (13) in 1915 made a classification of three types of fusiform bacilli and of six types of spirochaetes.

These findings have been confirmed and reconfirmed many times in the succeeding years, and very complete bacteriology, morphology and histopathology of not only the spirochaetes and fusiform bacilli are to be found in the literature, but also that of the various cocci which, if not always found, are very commonly present.

Despite these findings, the etiologic organism of tropical ulcer is still a question in the minds of many. That nearly every organism has, at one time or another, been blamed is probably at least in part due to the fact that most of these ulcers are not seen until late, a good history is hard to obtain and secondary infection and contamination is the rule due to the nature of the living conditions of the natives in the tropics. It is also very possible that a symbiosis of more than one or two organisms is necessary for the development of the ulcer as has been suggested by the work of Fox (15) which will be more fully considered later.

Another reason for this uncertainty as to the etiologic organism of tropical ulcer in the minds of many is because of the common occurrence of the spirochaete and fusiform bacilli in many superficial sores and abrasions. Loewenthal (27) states that for this reason the fact that spirochaetes and fusiform bacilli are constantly found in tropical ulcer is of no scientific value etiologically. He says it is exceptional for these organisms to be absent in any wound of the skin or mucus layers. Mendelson (32) in 1919 studied one hundred cases of ulcers, only 10% of which showed spirochaetes corresponding to the Spirochaeta schaudinni and therefore considered it to be a superimposed infection. He goes on to say that certainly this spirochaete was not limited to a disease of distinct clinical features, but found in diseases which varied widely clinically.

A third reason for discrediting the fusospirochaetal etiological theory is because of the difficulty of culturing the organisms and the difficulty of transmission of the ulcer by inoculation experiments. Loewenthal (27), in 1932, said that there had never been any evidence in the literature of more than one of Koch's postulates having been fulfilled to prove the relationship of the spirochaete to the tropical ulcer.

Smith (4) considered bacillus pyocyaneus responsible for at least some cases of the disease.

Fox (15) says that the most striking feature of a smear taken from the gray secretion of the tropical ulcer is the presence of enormous numbers of bacilli, mostly fusiform in shape. Associated are spirochaetes and in a few cases staphlococci, diplococci, and streptococci. Adams (1) states that streptococci are found in the pus at the floor of the ulcers while smears made from scraping the edges show fusiform bacilli.

A. Inoculation Experiments. In attempting to establish the etiology of tropical ulcer, isolation and inoculation of the organisms have been a major issue. Such attempts have been more or less unsuccessful up to the present time.

In 1915, Breinl (5) reported that direct transmission of the ulcer to experimental animals and to man was always unsuccessful. He states that Blanchard (3), the year before, had passed the disease from man to man, but only after first producing an area of artificial necrosis and then inoculating the material from the ulcer.

Fox (15), in 1921, in reporting his inoculation experiments comments that no animals were infected and only one man. This man had been infected from the ulcer directly. When the lesion first appeared it showed cocci with a few bacilli. Two days later, the slough

having increased, bacilli were predominant with a few spirochaetes. One day later the spirochaetes had increased enormously and but few cocci could be found. It was interesting that an ulcer resulting from the inoculation of the culture of streptococci and other cocci was atypical and that a culture of the bacillus alone inoculated intramuscularly was negative. It would seem that to produce a typical ulcer, the presence of both fusiform bacilli and spirochaetes are necessary, as are probably various types of cocci.

Since Loewenthal's statement in 1932, that never had more than one of Koch's postulates been fulfilled in relation to the etiology of tropical ulcer, E. C. Smith has been publishing the results of his inoculation experiments. Although his results have not as yet completely settled the question, they bring more and more evidence to bear upon the fact that the spirochaete and the fusiform bacilli have more than merely a passive role in the etiology of the ulcer. Smith published his first report in 1930 (40). At that time he stated that he had cultured spirochaetes from cases of tropical ulcer in a modified Wenyon media and that the culture had been successfully passed through thirty-two subcultures. A pure culture of the spirochaete was not obtained. Five inoculation experiments were described for which he used his spirochaetal culture. The

contaminating organisms were fusiform bacilli and those of the pseudomonas group. The experiment was conducted in the following manner.

1. Aerobic mixed cultures of the spirochaete and B. pseudomonas were inoculated into the arms of some of the subjects.

2. Anaerobic mixed cultures of the fusiform bacilli and B. pseudomonas were inoculated into the arms of other subjects.

3. Controls were run in the oposite arm with B. pseudomonas.

No general reaction was noted in any of the five cases. The controls were all negative. Ulcers were produced in all five cases which resembled tropical ulcer. Hospital patients were used for the experiment. The resulting ulcers were treated with dry dressings or hot fomentations.

Since pure cultures were not available it was impossible for Smith to draw any definite conclusions, but he showed that:

1. Spirochaetes in mixed culture are capable of active proliferation when inoculated into the skin of suitable subjects, and can produce lesions resembling tropical ulcer.

2. Fusiform bacilli free of spirochaetes can do the same thing.

3. B. pseudomonas are not able to produce lesions resembling tropical ulcer.

Again in 1923 Smith (42) isolated fusiform bacilli in pure culture from typical tropical ulcer which he inoculated into man. These experiments showed that a pure culture of a strain of fusiform bacilli grown in solid and semi-solid media, when inoculated intracutaneously into volunteers did not produce lesions resembling tropical ulcer, although, there was considerable evidence of toxic action. When experimentally inoculated into the skin the bacilli remained alive and motile as long as fourteen days after inoculation.

In 1936 Smith (43) reported the following results from experimental work on animals. He found that material from tropical ulcer, when suitably inoculated, is pathogenic for Nigerian hedgehogs, and spirochaetes and fusiform bacilli are present in the experimental lesions produced. Scrapings from ulcers emulsified in broth and examined for organisms were inoculated intracutaneously into the hedgehogs. In all animals inoculated a well formed bleb was present by the second day and the surrounding skin was inflamed and indurated. Ulceration occurred from the third to the fifth day. The ulcers varied in size from one to three centimeters in diameter and were oval or circular with hard slightly raised edges. In the early stage the floor was covered

with tenacious, gray-green, foul smelling slough. Partial or complete separation of the slough occurred from the fifth to the seventh day disclosing a purulent base composed of granulation tissue and necrotic material. The ulcers were usually all healed by the eleventh day. Two ulcers remained until the twenty-fourth day and three of the animals died about the seventh day. In six instances the ulcer was passed on from the first animal to a second one. In five cases the ulcer was transmitted a third time, in two cases it was transmitted a fourth time and in two others a fifth time, while in only one case was it passed on a sixth time. These succeeding ulcerations were in all instances the same as those previously described.

It is seen from the above experiment that lesions closely resembling tropical ulcer may be produced by spirochaetes and B. pseudomonas and by fusiform bacilli and B. pseudomonas, but not by the fusiform bacilli in pure culture or by B. pseudomonas in pure culture. A pure culture of the spirochaete is still to be obtained before it can be determined whether or not it can produce the ulcer. It seems very probable, however, that the spirochaete will develop only in the presence of one or more of these other organisms and that a symbiosis of more than one of them is necessary for the development of the tropical ulcer.

CHART I		
Morphological Classification of Fusiform Bacilli found in Tropical Ulcers Based on Eggers' Classification		
Type I		
Eggers '15	Walback & Todd'12	Fox '21
Violet Staining (May show large spherical central swelling)	Purple Staining	Gram Negative (with Giemsa some show irregular beaded appearance due to deeper staining granules.)
A. 6-12u x 1u cytoplasm uniform or finely granular may be slightly curved and form chains may become club shaped	large, thick with tapering ends clear spaces in the form of bars or vacules	thick, long leptothrical forms
B. 3-8u x 1u cytoplasm contains redish metachromatic granules symmetrically arranged and usually two in number. often curved		

CHART I (Con't)		
Type II		
Eggers '15	Walback & Todd '12	Fox '21
Clear Blue cytoplasm and reddish sharply defined granules	Stains Bright Blue with red dots	Light Blue
A. 4u x 0.5u Two metachromatic granules symetrically arranged		2.5u - 4u Tapered ends, and a few rounded ends
B. 6-9u x 0.5u more granules Symmetrical pairs	4 - 10u 2-6 granules singly or in pairs	slender curved rods maroon granules
Type III		
Eggers '15	Walback & Todd '12	Fox '21
Violet Stain Short & plump rounded ends Terminal flagellum		

CHART II		
Morphological Classification of Spirochaeta found in Tropical Ulcer Based on Eggers' Classification		
Eggers '15	Wolback & Todd '12	Fox '21
Type A.		
13 u (with variations)	10-18u x ½-1u	10-20u long
3 or 4 complete regular convolutions of considerable amplitude	5-7 spirals most commonly found	few wide coils
Bluish stain with Giemsa	Bluish-purple stain	Stains with dilute carbol fuchsin
Variations of Type A.		
1. Convolutions smaller more irregular (only found with A)	irregular spirals in some organisms. (taper abruptly)	More than one variety
2. Almost straight (only found with A)		
3. 17u, more convolutions with slight amplitude. (may be separate type)		

CHART II (Con't)		
Eggers '15	Wolback & Todd '12	Fox '21
Type B.		
longer and thicker than A. convolutions irregular Red or violet with Giemsa (ends taper abruptly)	long and thick Redish-purple (blunt ends)	
Type C.		
7u and thicker than A convolutions regular, of small amplitude. Red or violet with Giemsa	short and thick closed spirals Redish-purple stain	
Type D. (rare)		
1-1½ convolutions regular, great amplitude. Bluish violet.		
Type E (rare)		
7u very thick regular fine convolutions intense blue ends taper abruptly		

CHART II (Con't)		
Eggers '15	Wolback &Todd '12	Fox '21
Type F.		
7u irregular and fine convolutions. Bluish stain.		

B. Morphology. In considering the morphology of the micro-organism of tropical ulcer, the Eggers' classification will be used here as a basis for study and for comparison with other descriptions of the organism as this is the most complete and well defined. Eggers' classification (13) is based on a study of smears from unselected cases of ulcers of the extremities. These smears were gathered from all over China.

From Chart I it is seen that Eggers defines three types or classes of fusiform bacilli based upon the staining characteristics of the cytoplasm of the organisms. Types I and II have been subdivided into two groups each due to variations in size, shape, and granules of the fusiform bacilli. In Chart I an attempt has been made to correlate the descriptions of other investigators with those of the Eggers' classification.

Walback and Todd (45) based much of their description of the fusiform bacilli on the work of Keyesselitz and Mayer (26). Le Danteg's (11) description of the fusiform bacilli in 1884, in which he says the organisms were 7-12 microns in length and were straight or slightly bent, corresponds with Type I-a of Eggers.

Clements (9) describes two types of fusiform bacilli as seen under the dark field. Type I is 10 microns long, has a double contour and tapers slightly. It is slightly motile and seems to bend from side to

side. Type II is non-motile and appears only as a single line.

Adams (1) describes the fusiform bacilli as resembling diphtheria bacilli in shape, but not in stain. He relates that French physicians in North Africa supposed that it was the diphtheria bacilli and even injected ulcer patients with diphtheria anti-toxin serum with varying results, some curative, some useless.

Fox (15) describes attempts at culturing the fusiform bacilli. He was able to grow them only by the method of Krumwiede and Pratte (25). The organisms grew anaerobically and the colonies were all of one type with dark center and green-blue margins. Microscopically the individual organisms appeared to be the same as those seen from the direct smear. The culture gave off a fetid odor.

Eggers described six types of spirochaetes in his classification with variation in Type A. This classification has been outlined in Chart II and again an attempt to correlate the descriptions of Wolback and Todd and that of Fox with that of Eggers has been made. For the most part these workers appear to agree very well. Eggers states that it is the spirochaete which he has classified as Type A which is most commonly found in tropical ulcer and Corpus (10) found morphologically similar organisms in tropical ulcers which he believes

to be a very definite etiological agent. Prowazek's Spirochaeta schaudinni, which he described as the specific cause of the tropical ulcer, compares very closely with Eggers' Type A, except that it is less tenuous than the latter (13).

Eggers' Type A spirochaete is long, tenuous and has three or four complete regular convolutions of considerable amplitude. It is 13 microns long with some variations. It stains a blue with Giemsa, or occasionally a violet which is probably an error in the staining technique. There is considerable variation in individual organisms, and there is a variation in staining throughout the whole of the organism. The spirochaete may be thicker at one end than the other. There are spirochaetes of perfectly regular convolutions but which are much thicker with tapering ends. These were thought by Prowazek (24) to represent sexual forms. Prowazek's resting forms, spirochaetes with terminal nodules were also seen by Eggers. Occasionaly a terminal flagellum was present. The varieties or subdivisions of Type A are adequately described in Chart II, as are Types B, C, D, E, and F.

Walback and Todd (45) describe a spirochaete which they found in twenty cases of tropical ulcer. They also noted many variations in morphology and they classed their findings into three types. The spirochaete which

they classed as Type I was present in all smears. This organism stained more faintly with a bluish-purple color. It measured 10-18 x $\frac{1}{2}$-1 microns in size. There were usually five to seven spirals which were irregular in some instances. Both ends of the spirochaete tapered abruptly. Many were bent or curved, often to a right angle. Unstained areas occasionally occurred and sometimes it could be seen that the spirochaetes consisted of a central core which stained like chromatin and of a periplast which did not. Rarely, the whole of the chromatin was fragmented so that the spirochaete looked like a string of granules. Very rarely a terminal flagellum-like prolongation was seen. Spirochaetes with rounded swellings in their course occurred occasionally but terminal rounded ends were not seen. No effort to demonstrate an undulating membrane was made, but a few organisms showed a flattened or band-like appendage at the crest of the spirals. As a rule the spirochaetes were single, occasionally two or more were joined by their affiliated ends and rarely two were intertwined. Encysted forms were not seen. Types II and III are described in Chart II.

Chandler (6) describes the tropical ulcer spirochaete in stained preparations as being 12-25 microns in length, very slender, with loose open coils with six or seven coils to every 10 microns.

Under dark field Clements (9) has described four types of spirochaetes as follows:

1. Treponema microdentium which is 3-9 microns long, has tapered ends and four or five coils. It moves rapidly by rotary movement or by flicking each end. The coils remain fixed.

2. Treponema macrodentium which is 4-5 microns long with blunt ends and large fixed coils placed further apart. It lashes about vigorously, but little progress is made.

3. Treponema vincenti which is 8-15 x 0.5 microns in size. When in motion two distinct sets of coils are seen. There are twenty small fixed coils which remain unchanged with motion. A serpentine motion superimposes the second set of coils on the first. These reform and disappear.

4. Treponema buccale are 8-15 x 0.8 microns in size. They have a double contour under the dark field and move by screw-like actions. The coils are fixed.

The last two, Treponema vincenti and Trepenoma buccale resemble Eggers' Type A the most closely.

Numerous attempts have been made to cultivate the spirochaete Treponema schaudinni. Muhlens (33) was probably the first to obtain a mixed culture of

the spirochaete and fusiform bacilli with material taken from a case of tropical ulcer. After three subcultures the spirochaete died out. Sanarelli (38) cultivated spirochaetes from material derived from guinea-pigs which was identical with spirochaetes of tropical ulcer. Fox (15) cultivated spirochaetes anaerobically from the Naga Sore in India, and Tunnicliff (44) obtained cultures of spirochaetes from mouth lesions similar to the spirochaetes of tropical ulcer. Smith (40) gathered material for culturing from the serous fluid extruded from tropical ulcer. He incubated this material at 37° C. and made thirty-two subinoculations at intervals varying from four to ten days. The following are the observations made by Smith as to the cultural characteristics of the Spirochaeta schaudinni:

1. The spirochaetes are aerobic.

2. Optimum temperature for growth is 37° C. The spirochaete will also grow between 27° C. and 30° C.

3. Subcultures do best when made on the fifth or sixth days.

4. The organism will not grow in serum-agar stabs.

5. The organism will grow better in human blood media than in rabbit blood media.

6. Longevity of the spirochaete at 37° C. varies. There are usually no active forms after twelve days.

Smith was not able to obtain pure cultures of the spirochaete. To date there has been no report of a pure spirochaetal culture by any of the investigators. It is possible that the spirochaete requires the presence of other organisms for its growth.

There are varying opinions as to the relationship of the fusiform bacilli and the spirochaete. Tunnicliff (44), in 1911, after studying cultures and smears from ulceromembranous angina, ulceromembranous stomatitis and diphtheria of the tonsils concluded that fusiform bacilli and the spirilla are different forms of one organism, because after she had grown fusiform bacilli a few days filaments and spiral forms appeared which resembled the spirilla found in smears made from the mouth in conjunction with the above named diseases.

James (22) describes what he called a "filamentous form". He says this may be long and rather thick and may be seen dividing to form fusiform bacilli. These forms may be finer and show every gradation between a long straight form and a definite spirochaete. Some filamentous forms are exceedingly fine. Some smears seem to show every step between the common fusiform bacilli and the spirochaete via the filamentous forms,

as though they were all actually one organism.

Clements (9), writing as recently as 1936, tends to hold the opinion that the fusiform bacilli is the aerobic form of the spirochaete. He quotes Saranelli (38) who considered that atmospheric oxygen and associated bacteria change the spirochaete into a fusiform bacilli. This theory is not in accord with the finding of Smith (40) that the spirochaete is an aerobe and those of Fox (15), who was able to cultivate the fusiform bacilli, only anaerobe.

In 1930, Smith (40) stated that it was still to be proved whether the spirochaete and fusiform bacilli were the same organism or distinct from one another. In his experiments of 1933 (42), when he incoulated fusiform bacilli into the skin he states that the fusiform bacilli remained alive as long as 14 days and that no mutations into spirochaetal forms were observed.

In 1915, Eggers (13) could establish nothing definite concerning the relationship between the fusiform bacilli and the spirochaetes. The different types varied in frequency in different specimens apparently without rule. Occasionally one or more would be absent from a given specimen and in two smears no fusiform bacilli could be found, although Type A spirochaetes were present. Fusiform bacilli, especially Type II, have been found not infrequently without any spiro-

chaetes being present. Eggers believes the relationship to be one of symbiosis, probably non-obligative on the part of the fusiform bacilli and possibly mutually so.

Staphylococci, diplococci, and streptococci as well as other micro-cocci and bacilli of various kinds have all been seen at times in direct smears from the ulcers (15 & 45). They are all gram positive. In cultures sown directly from the ulcer the mixed growth invariably contains a streptococcus which appears to be very resistant and will thrive in practically any medium, both aerobically and anaerobically.

PATHOLOGICAL HISTOLOGY

GROSS PATHOLOGY. Tropical ulcer spreads over the surface of the skin and may involve all the tissues including the bone. Ulcers that have been neglected are blackish and contain disintegrated materials. Some are covered by thick, hard, elevated, whitish pseudomembranes. Some varieties are elevated or deeply depressed and in all cases the edges are undermined, smooth or ragged. The floor may be smooth or ragged also. In those with a ragged floor the ulcers are usually rounded or oval, but they may exhibit all varieties of shapes.

HISTOPATHOLOGY. Keysselitz and Mayer (26), in 1909, first described in detail the pathological anatomy of tropical ulcer. They pointed out three layers composed of cells, bacteria and debris, bound together with fibrin. In 1912, this work was confirmed by Walback and Todd (45) who emphasized the thickened epidermis surrounding the ulcer and stated that it was due to an increase in the prickle cell layer. Breinl's (5) work, in 1915, agrees very well with these findings and since then Smith (41) and Clements (9) have described very similar findings in spite of new and better methods of staining. All workers have, in a more or less specific manner, described the three layers as pointed out by Kyesselitz

and Mayer(26).

The first or most supperficial layer (pseudo-membrane) is a structureless matrix with countless bacteria, mainly fusiform bacilli. It is necrotic in nature and may have a greenish-gray appearance.

The second or deepest portion of the outer layer of the section of the ulcer stains more darkly. Under high power it is found to consist of fusiform bacilli arranged in a "palisade formation", which form a barrier between the structureless outer layer and the underlying tissue which still retains its structure. This palisade stops short of the epithelial borders of the lesion. The bacilli in this palisade were found to be arranged in closely packed perpendicular masses.

Smith (41) believes the massing of the fusiform bacilli close to the surface of the tropical ulcer lesion may be dependent upon the existence of anaerobic or partial anaerobic conditions in the superficial zone of dead necrotic tissue devoid of blood supply. In this connection it may be noted that the fusiform bacilli, when isolated in pure culture from the lesions of tropical ulcer are found to be strict anaerobes.

The spirochaetes on the other hand, have been cultured both aerobically and under partial anaerobiasis.

Clements (9) explains the histopathology of the ulcer in such a way as to support his theory that the spirochaete is an anaerobe when he says that the more strictly anaerobic spirochaetes are the active invaders of the new tissue, producing a certain pathological state which is followed by necrosis. The fusiform bacilli are content to foul the surface, no doubt, playing some part in the production of the pseudomembrane.

The third layer of the underlying tissue of the tropical ulcer is invaded by polymorphonuclear leucocytes, of which the greatest concentration is to be found near the barrier of the fusiform bacilli palisade. This layer appears only in actively extending areas of the ulcer. In experimentally produced ulcers it was possible to demonstrate that an ulcer spreads irregularly and only in small limited areas. The histological appearance of that portion of the base of the ulcer which is not spreading is simply that of a mass of granulation tissue (9). The spirochaetes are found invading the granulation tissue of the base of the ulcer. They tend in places to follow the course of the capillary loops of this tissue. Here and there the spirochaetes are found embedded in the delicate walls of the vessels, and they are also found free in the lumina (41). The presence of spirochaetes within the capillaries is an

added proof of the invasive tendency of these organisms and suggests that they may be present in the blood stream during life. The malpighian layer of the epithelium in the neighborhood of the ulcer margin is, as a rule, densely infiltrated by the spirochaetes. Smith believes the spirochaete advances further into the healthy tissue than does the fusiform bacilli and Hollenberger (18) claims that the fusiform bacilli extend into the tissue in advance of the spirochaete.

Much of the disparity which exists in the recorded descriptions of the distribution of the organisms in the lesion of tropical ulcer is probably due to the examination of tissues from ulcers of widely varying duration (41). In the very young ulcer, the organisms usually occur as a superficial membranous-like layer without any marked differentiation as regards location. In the older lesions the condition is generally one of partial healing by granulation tissue with a superimposed secondary infection. It is in the actively progressive lesion of from two to four weeks' duration that a true conception of the relative invasive powers of the two organisms may be obtained.

(41) To summarize the distribution of the organisms in tropical ulcer: spirochaetes, fusiform bacilli, and innumerable bacteria are found on the surface and in the exudate, while large masses of fusiform

bacilli lie close to the surface of the ulcer. The spirochaete is occasionally found in the granulation tissue at a considerable depth, but mostly lying on the surface between other micro-organisms or between the epithelial cells adjoining the ulcer. (5)

Walback and Todd (45) have given a very detailed description of the pathological anatomy of the tropical ulcer. The conspicuous features of the histology of the ulcers regardless of great differences in the duration of the ulcer process are proliferative changes in the epidermis and the production of granulation tissue with marked lymphoid and plasma cell accumulations.

In early cases the epithelial change is most pronounced. Thickening is due chiefly to an increase in the prickle cell layer. In upper layers of epidermis the cells are swollen and separated by spaces bridged by intercellular processes. The nuclei are preserved in the horny layer. The epithelium is heavily invaded by polymorphonuclear leucocytes. The "palisade layer" is represented by a layer several cells deep with irregular arrangement, and containing numerous mitoses. When the epidermis at the center was wiped away before excision it separated cleanly from the edematous papillae of the corium. Beneath the epidermis adjacent to the denuded area there were spaces where the epidermis had

been lifted from the corium by an exudate containing red blood cells, a very few polymorphonuclear leucocytes, and some fibrin. The corium was edematous, particularly in the papillary layer. In the deeper layer there was extreme infiltration with lymphoid and plasma cells, with plasma cells predominating. The accumulations were more dense about the vessels and gave a lobulated appearance when viewed under low power. In addition to lymphoid and plasma cells there are large numbers of eosinophils in the vicinity of the small vessels. There are a few polymorphonuclear leucocytes everywhere in the corium, but there is no suggestion of a suppurative process. In the sub-papillary layer where the infiltration is less extreme, the edematous corium contains numerous fibroblasts.

The chronic ulcers have practically the same conditions at the periphery of the lesions as those seen in the early cases. The changes in the epidermis are absent or masked when regeneration of epithelium has taken place. The ulcer itself consists of granulation tissue in which there is nothing distinctive. The deeper tissues and corium surrounding the ulcer show heavy lymphoid and plasma cell infiltration. In most ulcers plasma cells predominate. The surface of the ulcer is covered by a tenacious membrane of spirochaetes and bacteria, or by a layer of coarsely meshed

hyaline fibrin in which masses of spirochaetes and bacteria are found. The epithelium surrounding the ulcer shows the usual thickening and down-growth, which is found in all chronic ulcerative processes. In a few cases, however, especially in ulcers of comparatively short duration, there is a thickening of the prickle layer. Spirochaetes in the epidermis support the view that the process is a reaction to some agent other than the ulcerative process alone. The spirochaetes are found in the epidermis, on the surface of the ulcers, and in the granulation tissue.

Breinl (5) has described sections from the boarder of the ulcer bed. These show hypertrophy of the epithelial layer which is many times the normal thickness. Between epithelial cells were roundish or oval, well-defined spaces of varying size, filled with loose and edematous fibrous tissue, in which polymorphonuclear leucocytes were imbedded. Epithelial strands between spaces became thin, cells became degenerative by increasing in size and becoming more vacuolated. The nuclei became irregular in shape and disappeared. In close proximity to the ulcers these spaces were densely packed with leucocytes and lymphocytes, resembling microscopically small abscesses. The superficial epithelial cells from the edges showed degenerative changes. The cytoplasm was vacuolated and the nuclei

were irregular and did not stain evenly.

Clements (9) states that the extending edge of the ulcer invades and destroys the stratum mucosum, while the stratum germinativum, which seems to escape the attack at first, stands out prominently in some sections amidst the surrounding destruction. The outline of the epidermis persists for some distance behind the head of the ulcerative process, indicating the intensity and rapidity of the destructive force.

James (23) and Fox (15) have done some very interesting work on the bacterial findings in smears taken from various types of the ulcer and from various stages of the development of the ulcer.

James classifies his findings in a general manner as follows:

1. Acute ulcers, show fusiform bacilli 100%, spirochaetes 75%, filamentous forms* 65%.

2. Clean, chronic and septic ulcers never show any of the above mentioned organisms.

3. Subacute ulcers show fusiform bacilli 82%, spirochaetes 50%, and filamentous forms 31%.

He further subdivides his classification into

*James filamentous forms have been described on page 36.

a. Messy, feted, superficial ulcers which show fusiform bacilli and spirochaetes.

b. Chronic ulcers of the toe nail area showing fusiform bacilli and spirochaetes.

c. Dark red ulcers with thin pale pus which show only fusiform bacilli.

c. Deep subcutaneous extensions showing fusiform bacilli only. Under this last group are, 1. deep ulcers with raised edges, 2. progressive ulcers, and 3. the serious type which extend along the fascial plains.

Drawing his conclusions from these results, James considers the fusiform bacilli ulcer to be a less rapid one, while the spirochaete in the ulcer seems to add virulence to the process, especially superficially.

In considering the bacterial findings in smears of ulcer at various stages of their progress James (23) has described the following stages:

Stage I. The idiopathic ulcer which is characterized by a painful vesicle. The contents are a dirty gray and the floor is moist and gray. Smears and cultures show only gram positive diplococci and staphlococci. When at this stage the ulcer is treated with a caustic there is immediate healing.

Stage II. Lesions of the above type just after breaking show fusiform bacilli and cocci of various kinds.

Stage III. A fully developed ulcer which had its beginning in a blister similar to Stage I and had broken twenty-four hours before showed fusiform bacilli, spirila (spirochaetes) and filamentous forms.

Stage IV. Cessation of phagedaenic process. Spirochaetes and filamentous forms disappear first. Fusiform bacilli become shorter and then disappear.

Stage V. Possible recurrence in a clean ulcer shows first fusiform and filamentous forms and later the recurrence of fusiform bacilli and spirochaetes.

Fox (15) believed it to be of significance that the bacilli and spirochaete were present in large numbers only when the dirty gray secretion, or false membrane was present, and that these organisms disappeared as the secretion cleared up.

Walback and Todd (45) consider the character of the pathological processes of tropical ulcer and certain clinical aspects, such as its location on exposed and vulnerable parts of the legs, and its occurrence singly, to be compatible with our knowledge

of the spirochaete and fusiform bacilli infections in general. They also believe that these factors support the explanation that the process is a reaction to an organism having but slight powers of invasion.

RELATION OF TROPICAL ULCER TO OTHER FUSO-SPIROCHAETAL DISEASES

The fuso-spirochaetal relationship, whether it be a symbiosis or two forms of the same organism, is found in diseases other than tropical ulcer. The causative organism of a number of these can not be differentiated from one another when not seen in conjunction with the disease process. These same diseases also have certain similar clinical features.

Mal-de-bacs (disease of the mouth) in Central America, noma or gangrenous stomatitis, New Guinea mouth disease, balanitis, Vincent's angina and certain diseases of the respiratory tract are all characterized by the presence of spirochaetes and fusiform bacilli in partnership.

Gunther (17) says that the New Guinea mouth disease and tropical ulcer differ only as to the site of occurrence; each is fundamentally due to food deficiency; each presents a foul, sloughing ulcer; from each can be isolated a spirochaete and a fusiform bacilli; each responds to the same form of treatment. Both diseases are almost entirely confined to natives. In its preliminary stages the New Guinea mouth disease is a disease of the gums and in its final stages it involves the cheek. There may be ulceration of the soft tissues of the hard palate with or without

perforation and the tonsils and uvula may be involved. The great danger is erosion of the larger vessels and death from hemorrhage.

The description of the New Guinea mouth disease very closely resembles that of noma, otherwise known as gangrenous stomatitis or cancrum oris. It may be present in other parts of the body besides the cheek, such as the ear, nose, genitals and anus. It is a rare disease which occurs in young children who are undernourished or who have undergone some debilatating disease as typhoid, measles, pneumonia (16). The part attacked is usually the seat of previous local disease. It begins in a spot on the inner surface of the lip or cheek and spreads outward and to the surface. The gangrene is always more extensive than it appears on the surface which is a matter of importance when treatment is considered. It destroys bone and soft tissue and has a terrible odor. There is no limit to the spread of the gangrene (24). Holt and McInosh (20) call it a malignant form of the infection produced by the Vincent's bacilli which are always present with a spirochaete. In the later stages numerous organisms are present, but in the beginning necrosis only the fusiform bacilli and the spiral forms are seen. The symbiosis is identical with that of tropical ulcer. Bonafede (4) has treated this disease with

oxidizing agents and intravenous sulpharsphenamine with some response. Holt and McIntosh advocated excision of the gangrenous area with cautery, but the disease is almost invariably fatal.

Reference has already been made to the close resemblence of Treponema schaudinni with Treponema vincenti and to the fact that Noguchi considered them to be the same organism. Clements (9) and others have also noted this similarity.

It is of more than passing interest that the classification of spirochaetes made by D. T. Smith (39) from organisms found in diseases of the mouth and respiratory tract were shown to be morphologically identical with those found in tropical ulcers. Almost all of the ulcers examined in Papua by Clements showed these types of organisms to occur in about equal numbers although occasionally Treponema vincenti appeared to predominate, a fact that had no relationship to the clinical appearance of the ulcer.

Clements (9) makes note of an interesting relationship between the pathological changes in the skin in pellagra and in tropical ulcer.

SOURCE OF INFECTION. Adams (1) says that if the causative organisms of tropical ulcer are harbored by a host other than man, it is not known. The carrier also has not been traced. The fact that the

disease occurs only in the dry season would be a point against the mosquito and suggest the sand fly, horse fly or some other summer insect as the carrier. The cases occur almost invariably among the poor people who do not or can not afford to sleep under nets.

Clements (9) has found the spirochaete and fusiform bacilli in the mouths of many natives of New Guinea (not, however, normal mouths). He believes that about 25% of the mouths of the inhabitants of the island of Manus are infected. He thinks that there are two common modes of infection in New Guinea. One is expectoration, which is promoted chiefly by the habit of betal nut chewing. The natives continually spit regardless of place or time. This saliva may land on anothers legs or on the grass or shrubs which later come in contact with bare native legs. The other method of transmission is probably by the native method of treating wounds. They seal chewed grass over the incised area or traumatized region with a leaf. This makes a wonderful inoculation as it introduces the organisms under the skin and produces anaerobic conditions under which they are believed to thrive best. Clements also believes that it may be possible for the ulcer to be transmitted by organisms carried on the feet and proboscides of non-biting flies such as the musca.

In Assum, Fox (15) claims that epidemics of Naga sore are associated with a plague of small flies which seem to be carriers of the infection. He says that a Dr. Hall Wright actually infected himself through the bite of one of these flies.

Corpus (10) states that the disease is contagious, being usually found among school children who are in constant contact with one another.

DIAGNOSIS

Although Corpus (10) says that there is no particular feature about the diagnosis of tropical ulcer, Innes (21) sets down the following diagnostic points:

1. Acute looking ulcer of long duration.
2. Punched out and undermined edged (not straight down as in syphilitic lesions).
3. Discharge of gliary mucus nature.
4. Free bleeding and pearly islets projecting through the base of the ulcer.
5. Pain in the acute and subacute forms.
6. The presence of Spirochaeta schaudinni and of fusiform bacilli.

Manson (29) states that tropical ulcer must be differentiated from yaws, syphilis, Oriental sore, varicose ulcers and veld sore. However, he says the differentiation is usually very simple and is made by exclusion.

TREATMENT

PROPHYLAXIS. As in any other disease prophylaxis is the most effective means of treating tropical ulcer. The following rules for prophylaxis have been cited by Clements (9):

1. Improvement of the general nutrition.

   a. In New Guinea this has been accomplished by regulating the diet of the native hired help. Marked decrease in the incidence of tropical ulcer occurred in such instances.

   b. There is the necessity of education of the natives to a better diet and how to obtain it.

2. Removal of the source of infection.

   a. The chewing of the betel nut is an unbreakable habit.

   b. James (23) and Corpus (10) suggest the wearing of shoes and stockings, since they have noted a marked difference in the incidence of tropical ulcer among school children who go barefooted and those who do not.

   c. Corpus (10) suggest that infected children should not be allowed to come in contact with other children. In the schoolroom they should be separated from the others but

not excluded.

3. Care of simple wounds.

a. Prompt attention to small scratches and cuts with soap and water and iodine.

b. Chewed grass treatment of wounds and the sucking of wounds should be discouraged.

4. James (23) has added the avoidence of malaria among the foreign element, at least, both by taking quinine and sleeping under nets. It might be suggested that if nets are to be slept under they should be of a sufficiently fine mesh to keep out the smaller insects as the sand fly as several investigators consider that these may be carriers rather than the mosquito.

GENERAL TREATMENT. There are as many types of treatment for tropical ulcer as there are writers upon the subject. Rarely do two of them agree on a method which is most effective. This fact strongly suggests that no truly effective treatment is as yet known.

Adams (1) has well stated the objective of treatment in tropical ulcer. He says it is to destroy germs without too great irritation of the already inflamed and abused part, to break down the cord-like ring of sclerotic tissue, and to stimulate the tissues

to a healthy reaction and healthy granulation. The region should be protected from further invasion of cocci, flies, dirt, and the epithelial growth and healing should be stimulated. He goes on to say that with the best of care considerable time is required for the healing of the ulcer and that a pigmented scar always remains.

Clements (9) gives a criteria for the measurement of the effectiveness of treatments. He says the method generally used was to compare the average number of days spent in the hospital by tropical ulcer patients before and after the introduction of the method of treatment under consideration.

In general, the treatment of tropical ulcer is begun by improving the diet. This, in some form or another, is emphasized by nearly everyone. Gunther (17) advocates a diet rich in vitamins, no rice, plenty of fresh vegetables, cod liver oil and rest. Clements (9) does not believe that cod liver oil or yeast are of any particular value. He has shown experimentally, however, in rats that, with removal of crusts and feeding of high vitamin diets, the rate of recovery from tropical ulcer was increased greatly. Clements adds, however, that though vitamin deficiency is a cause or a predisposing factor in tropical ulcer, the feeding of vitamins does not heal the ulcer without other local

measures. This is also borne out by other investigators. Manson (29) thinks that lime juice and quinine are of value in the general treatment of the ulcer. As well as these, he also advocates opium in full doses, not merely to assuage the pain, but on account of its special action on the phagedaenic process.

Corpus (10) includes clean homes and sanitary surroundings, clean clothes, frequent bathing, and fresh air among the important factors in the hygenic treatment.

In extreme cases, James (23) has advocated blood transfusions and amputations as life saving measures.

Arsenicals have been used in various ways with greatly varying results. Heath (19) gave injections of arsphenamine, with KI by mouth and local treatments of 0.5% creosol to the ulcer. He reported that besides a marvelous quickness with which the ulcer healed, a striking feature was the appearance of improvement in the general health and appearance of the patients. Breinl (5) reports excellent results with salversan, but says it is expensive and complicated. Corpus (10) has used a 3% solution of arsphenamine locally on the ulcer site with what he considered to be very good results. He saturated cotton with the arsphenamine and placed it over the ulcer. This was allowed to remain

for twenty-four hours at a time. When healthy granulation tissue showed, the ulcer was washed with a solution of creosol and dusted with boric acid until cured. Corpus states that the granulations usually begin to show up during the first or second day of treatment and the discharge diminished in one or two days.

Clements (9) is very skeptical as to the results reported by the use of arsenicals. He is inclined to believe that the lesions so reported were frambesia rather than tropical ulcer. He stated that present-day experience has shown no effect of arsenicals on the tropical ulcer. He says that vaccine thereapy, also, is of no avail.

For a good many years there has been an undercurrent of opinion that tropical ulcer is associated with low calcium blood level and that calcium chloride injections are of great value therapeutically. Price (36), McCulloch (30), Lovett-Campbell (28) and Loewenthal (21) are among those who held to this opinion. Loewenthal treated tropical ulcer by daily intravenous injections of 15 grains of calcium chloride in 10 cc of distilled water for adults and 5 to 7 grains of calcium chloride for children, with a local eusol dressing b. i. d. His results were a disappearance of the offensive odor in two or three days. He is positive that this was not due to the eusol dressings

as these had been used alone with no results. At the end of the first week Loewenthal reported a separation of the slough and an appearance of a healthy granulation tissue. The diseased bone also separated spontaneously. In ten days' time the slough was clean with no exceptions. Healing began from the outside and usually was rapid. The general condition of the patient improved with the healing of the ulcer. He reported 84% of the cases so treated as having been improved or cured.

Ellis (14), in 1936, very carefully studied the relationship of blood calcium levels to the incidence of tropical ulcer, and he could find no significant correlation between the two. He obtained no satisfactory results by intravenous injections of calcium salts and believed it to have no rational theropeutic basis. Gunther (17) also reports disappointing results with the calcium treatments. Clements (9) found that sufferers from tropical ulcer in the New Guinea islands had a rather high calcium blood level and he was not able to see that calcium injections were of any benefit.

LOCAL TREATMENT. In the local treatment of ulcer a great variety of methods and substances are used.

Cautery is a method which has been cited by Corpus (10) and consists of scraping away all the slough and softened tissue and in cutting away all necrosed edges. Loewenthal (27) says that scraping of the bone with removal of necrosed tissue may bring about a slow healing but more often it has no effect. Brienl (5) advocates the removal of the granulation tissue with a sharp spoon followed by dressings of iodoform boracic acid 1-10. He believes this to be a very good method.

James (22) has worked out a method of excision of the ulcer followed by skin graft. He has found this to be very successful, not only because of reduced hospitalization but also because the ulcers so treated seem to stay healed. James found the seed graft to be the surest and the most easily applied method, but in some cases he combined the Thiersch graft with the seeds. The following are among the methods he used:

1. Curettage of ulcer and the application of seed grafts.

2. Cleaning of the ulcer first by medical methods followed by applications of Thiersch or seed grafts to the ulcerative bed.

3. Excision of the ulcer and after an interval of several days skin grafting.

4. Excision of the ulcer and immediate

grafting. This last method proved to be the most successful.

The average time taken for complete epithelialization of the area was thirteen days. In 45 cases 91% were completely successful, 7% partially so, and 2% were non-successful.

Gunther (17), in 1938, used copper sulphate for the treatment of tropical ulcer and for the very closely related New Guinea mouth disease. He says that in local treatment of tropical ulcer copper sulphate acts with such rapidity in comparison with other forms of treatment that it can be regarded as a specific. He says it is best used as a solution of 1-150 approximately, or 1 level teaspoonful of crystals to a 26 oz. bottle. This may be applied as wet compresses to the ulcer or as a mouth wash in the New Guinea mouth disease. He treats the ulcer in one of two ways. Lint is soaked in the copper sulphate solution and applied very wet to the ulcer every four hours until the slough disappears. Then the compress is applied only every twelve hours, but it is kept moist all the time. When good granulation tissue has developed scarlet red and adhesive tape are used. The slough usually disappears in thirty-six hours and in about ten days the ulcer is ready for adhesive. If the area is very extensive, skin grafting is advisable. A fragile, non-pigmented scar is

the result. In his second method, Gunther starts out in the same manner as in the first method until after the slough has taken place. He then uses copper sulphate baths and in two or three days, when a granulation tissue has developed, he excises the whole ulcer and sutures the area with silkworm gut. Gunther has noted no ill effects from absorption or swallowing of the copper sulphate solution which he uses. The healthy mucus membranes do not seem to be affected. The material is easily dissolved and the crystals are easily transported and to not deteriorate and are cheap. Gunther also says that when copper sulphate is used there are no relapses, but otherwise it is typical for an ulcer which is apparently clean and healing well, even at the stage in which the skin is advancing over the granulation tissue, to break down over night so that it is larger than the original ulcer.

James (23) describes a treatment other than that of skin grafting. The fundamental principles involved are eradication of infection and encouragement of epithelization. He uses a lotion which was first described by McGuire (31) in 1934 and which is composed of 1 oz. of a saturated solution of copper sulphate to one dram of pure carbolic acid as an anaesthetic. This is applied daily until the surface is hard and granular. Acroflavine (1/100) and hot fomentations are then used

until the ulcer is clean, when clean scarlet red and adhesive plaster are used for one week. If the ulcer is very large, incision and skin grafting is the best method. In ulcers of long standing the scar tissue is removed in fleshy areas, a "V" shaped incision is made and the skin edges are easily sutured. Where scales are present, excision and grafting are again the best procedure. When bony surfaces are involved, James says that the skin never heals over and it is necessary for the patient to always wear a bandage.

Corpus (10) used a method of saline injections with rather good results. The ulcers were thoroughly curetted and wiped off with sterile 0.6% NaCl solution. A 20 cc. syringe was filled with the solution which was injected beneath the ulcer, the needle entering at the margin of the ulceration and going deep enough to prevent the solution from oozing out. The ulcer was then covered with sterile gauze saturated with the solution. These injections were given daily as long as the ulcer persisted. Every case so treated responded. In the majority of cases, the cure was rapid and permanent. The old edematous tissue surrounding the edges of the ulcers disappeared rapidly, and was replaced by healthy tissue. The discharge ceased, new healthy granulations soon covered the ulceration and healing resulted.

Corpus (10) describes two other methods of treatment. One is with what he calls Vincent's powder. It is 1 part sodium hypochlorite and 9 parts boric acid and is, in his opinion, the most effective drug used. The ulcer is washed with a 1/4000 solution of potassium permanganate and dusted with Vincent's powder. The discharge decreases and granulations appear in four to six days. The ulcer is washed with physiological salt solution and zinc oxide is applied until healing takes place. The second method described by Corpus is by the use of mercurial ointment which, he says, is of little use.

Manson (29) also mentions several methods of treatment. He scrapes the surface until healthy granulations appear or applies formalin lightly once a day followed by a bismuth paste as soon as a scab is formed. He also advises tars preceded by a washing of the ulcer with eusol and followed by zinc. For small ulcers he uses iodoform and a firm bandage. He says strapping with elastopast without a dressing to allow the pus to escape through the bandage encourages epithelialization to take place on the edges of the ulcer. Zinc ionization then is useful in healing up residual areas of ulceration.

Innes (21) describes a treatment which she has used for some in India with a rather marked degree of

success and which is also quite simple and cheap. Quinine sulphate in powder form is first thickly dusted over the ulcer. Cinchona powder is then applied to the ulcer and the patient is given enough cinchona to last him for about four days, at the end of which time he is to return for another quinine dusting and more cinchona. Before the second application of quinine, the old powder is removed painlessly by applying a cold sodium bicarbonate solution (2 drachms to a pint of water) to the sore by cotton pledgets. The pain of the ulcer is usually relieved in half an hour after the first dressing and the ulcer heals in from two to four weeks. Innes says that KI should not be given internally in any case of tropical ulcer as it causes the ulcer to spread.

Clements (9) believes that oxygen liberating drugs are superior to others in healing tropical ulcer as they have more of an effect on the anaerobic spirochaetes. He also thinks the use of hypotonic saline baths are of value. He has tried X-ray and has found it to be of no help whatsoever in treating the ulcer.

None of these methods of treatment have, as yet, been reported as having been as successfully carried out by a second worker as by the originator. The only possible exception is the method of excision and skin grafting, but even this procedure is not

advocated with great enthusiasm by all workers in the tropics.

CONCLUSIONS

1. Tropical ulcer is the result of a fuso-spirochaetal symbiotic infection more apt to occur in individuals suffering from malnutrition or from vitamin dificiency.

2. Calcium plays no part in the etiology or treatment of tropical ulcer.

3. To date there is no known generally effective treatment for tropical ulcer. Excision and skin graft is the only method of treatment found by more than one worker to be of much value.

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